Multiple Sclerosis - notes

Pharmacy (University of Hertfordshire)

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MULTIPLE SCLEROSIS:

AIMS:

- Describe the pharmacology and clinical impairments of types of multiple sclerosis (MS)
- Understand the mechanism of action and limitation of drug used to treat relapsing and remitting MS

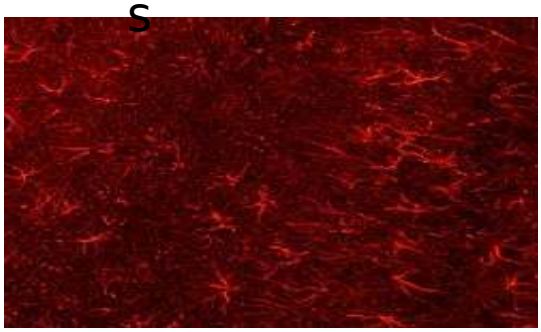
- MS is a neuro-inflammatory disorder → it is in the CNS – which is the brain and the spinal cord
- T-cells drive this disease but have to cross BBB to do so
- Neurological symptoms occur due to the damage to the axons

CELL TYPES IN THE CNS: - other than neurones

- There are 4 types of other cells in the CNS:
- Astrocytes
- Microglia
- Oligodendrocytes
- Ependymal cells

ASTROCYTES:

astrocytes



- There are 10 times more of astrocytes than neurones
- Astrocytes are very important in **cell repair** – in MS the astrocytes can be seen in MRI scans, when you diagnose a patient you see multiple scars
- MS – sclerosis means scars in Latin

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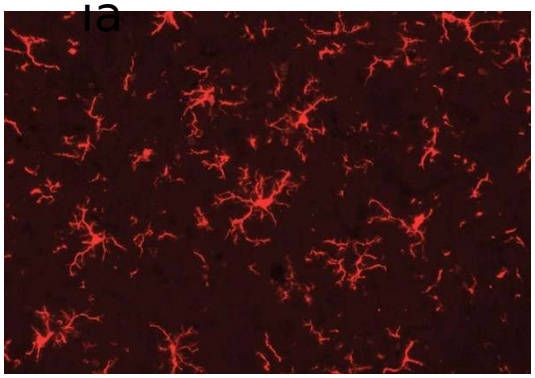
microgl
ia

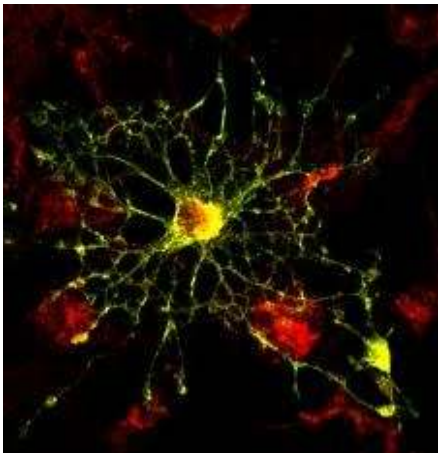


- What is left behind from damage are these astrocytes

MICROGLIA:

- Found everywhere in the CNS
- They are the brain “macrophage”
- As there are no T or B cells in the CNS -the only immune cell in the CNS is microglia
- Microglia are phagocytic cells
- Whenever there is damage in CNS (e.g. due to trauma or neurodegenerative condition) then the microglia cells are activated and come along to engulf the cells causing damage.

OLIGODENDROCYTES:



oligodendrocytes

- These are the cells that **degenerate** in MS (the cells that are damaged)
- Has similar function to a Schwann cell
- Oligodendrocytes – myelin producing cell that wraps around the axon and helps with conduction
- **Same function as Schwann cell;** but in peripheral nerves it is called a Schwann cell but in the CNS, it is called an oligodendrocyte.
- It produces myelin – **wrap around axon to help with conduction**
- These are damaged in MS – when damaged it slows down the conduction during neurotransmission
- Form the insulating myelin sheath that surrounds many axons
- Increases efficiency of nerve propagation
- In PNS = SCHWANN
- In CNS = OLIGODENDROCYTES

Ependymal cells

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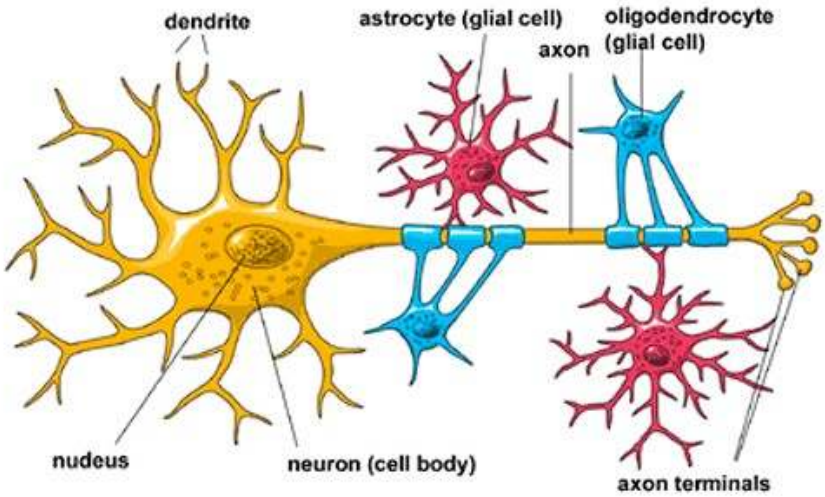
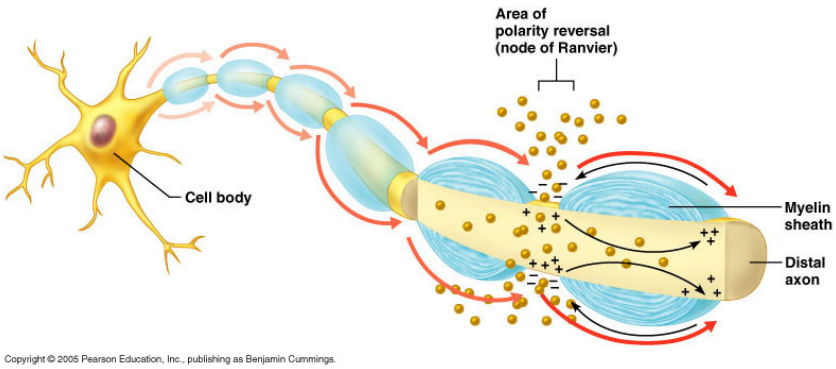
EPENDYMAL CELLS:

- Line the ventricles, CSF
- These are like ciliated cells
- Facilitate the movement of the cerebrospinal fluid (CSF)
- Interact with astrocytes to form the CSF/neuronal barriers of brain/spinal cord



OLIGODENDROCYTES:

- Oligodendrocytes are the myelin cells and enable axonal conduction
- A unique specialisation of glia in vertebrates is the deposition of myelin


Area of polarity reversal (node of Ranvier)
Cell body
Myelin sheath
Distal axon
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- They wrap long segments of axons with **a multi-layered sheath** of extended cell membrane
- Myelin was first understood to enable **saltatory conduction** impulse propagation in axons.

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- There is a high density of potassium and sodium channels in gaps between these cells (nodes of Ranvier)
- HIGH density of Na+ channels – these sodium channels allow generation of action potential which jumps from node to node
- Axon is insulated via myelin so there is no leakage of positive ions from the axon – DEPOLARISATION is propagated down the axon

If there is damage at the axon – process of saltatory conduction slows down

MULTIPLE SCLEROSIS: LOSS OF MYELIN IN THE CNS

- First described in 1868 by Jean Martin Charcot
- MS is a common auto-immune inflammatory de-myelinating disease → it only effects the myelin in CNS
- It is characterised by loss of myelin. Gliosis scar, failure to re-myelinate and consequential
- Affects around 100,000 people in the UK
- Usual onset 20-40 years of age
- As a result of the loss of myelin – you get astrocytes coming in (what is left behind – scars)

DIFFERENT TYPES OF MULTIPLE SCLEROSIS:

- Relapsing remitting MS
- Secondary progressive MS
- Primary progressive MS

- The most common type of MS is **relapsing remitting MS** – you get a relapse as you get damage to the cells and then you get remission when you get re-myelination.
- Unlike neurones, in oligodendrocytes can regenerate (re-myelination) they can be replaced/repaired. This is why people go into remission.
- Patient can stay in remission for many years – as you get remyelination

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- Over time, you can have failure to re-myelinate. This is when patients can go into the PROGRESSIVE stage
- MS is an early life disease

- Patients may present with a neurological problem; as MS affects myelin cells (white matter) → symptoms in brain stem, bac of cortex, cerebellum, visual cortex (vision loss), tingling, loss of balance

MS CLINICAL SUBTYPES:

Relapse-remitting MS → 80% at diagnosis (most common form)

- More common – can lead to progressive
- Symptoms can be present for number of weeks, and stay very stable (the symptoms do not get worse) but then they can go into remission
- It could be many years before patient has another relapse
- Approximately 50% of relapse-remitting will go into secondary-progressive after 15 years and 80% after 25 years.

Secondary progressive MS → patient is relapse-remitting and then their symptoms gradually worsen and they do not go into remission

- May get re-myelination of some cells but not getting re-myelination so this exposes the axon to damage
- There is a significant amount of de-generation
- Without re-myelination (repair of these cells) the axon becomes exposed and damages.

Primary progressive MS → patients present with symptoms that progress form the onset (they do not have relapse-remitting at all; no re-myelination

Progressive relapsing MS → very rare

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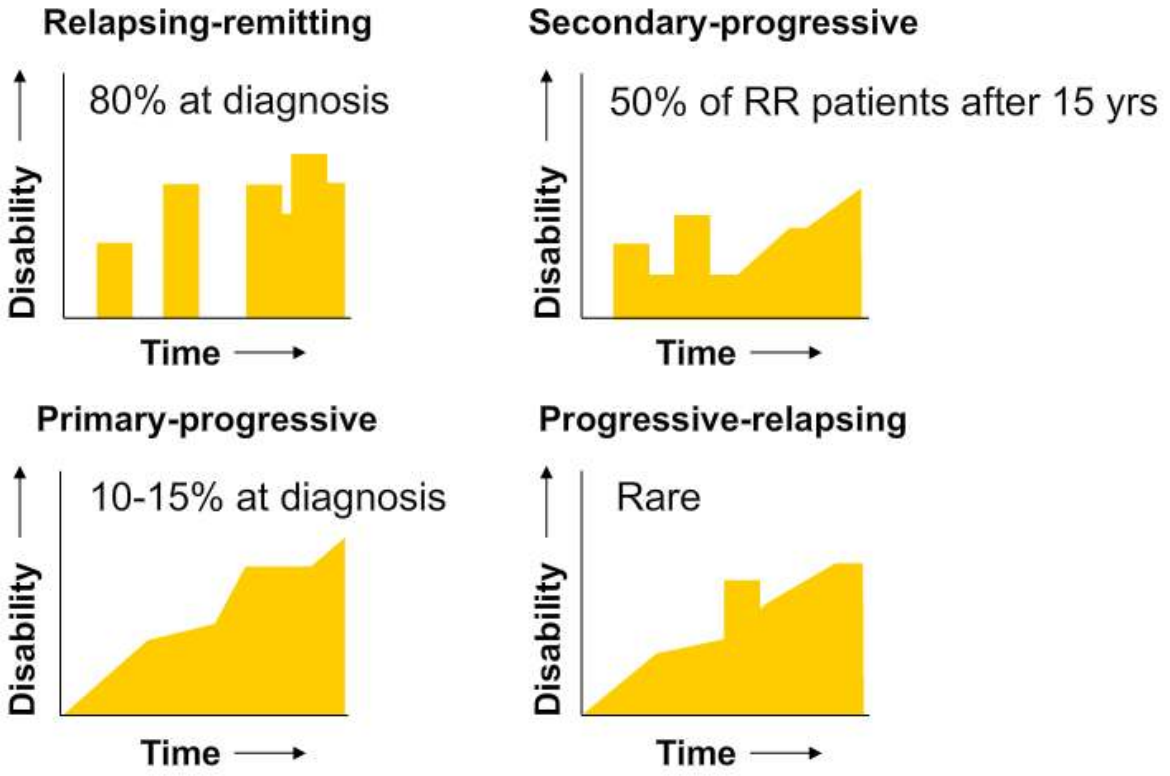
Patient has progressive MS and relapsing on top of that



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OLIGODENDROCYTE DEMYELINATION AND RE-MYELINATION:

- Oligodendrocytes wrap around axons to help with conduction
- In relapsing-remitting MS – there is damage to these cells
- The T-cells target oligodendrocytes and kill these cells

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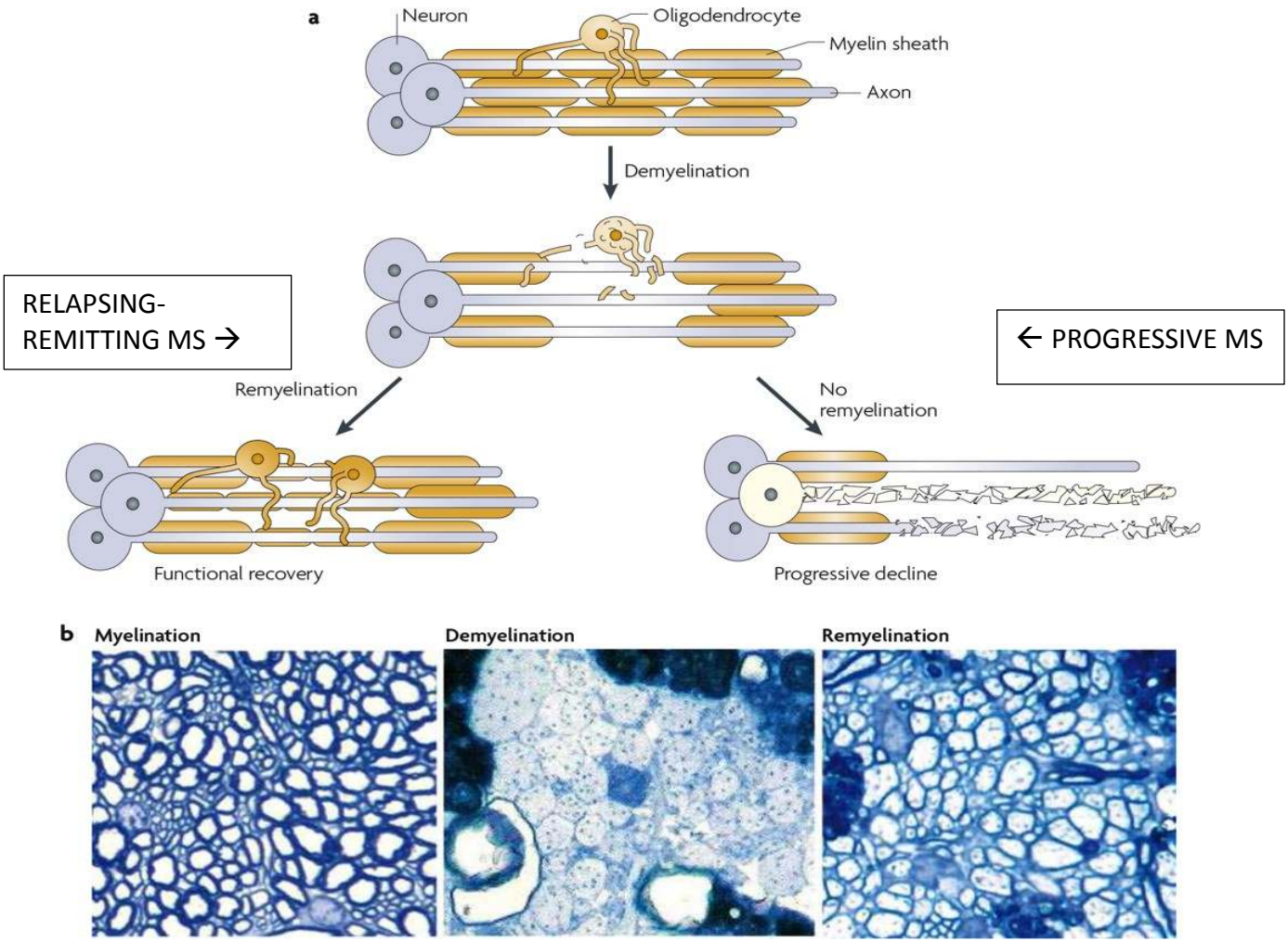
- The cells can re-myelinate and repair (unlike neurones)



DEMYELINATION IN MS LEADS TO LOSS OF SALTATORY CONDUCTION

- This results in neurological symptoms
- Symptoms are entirely related to the location

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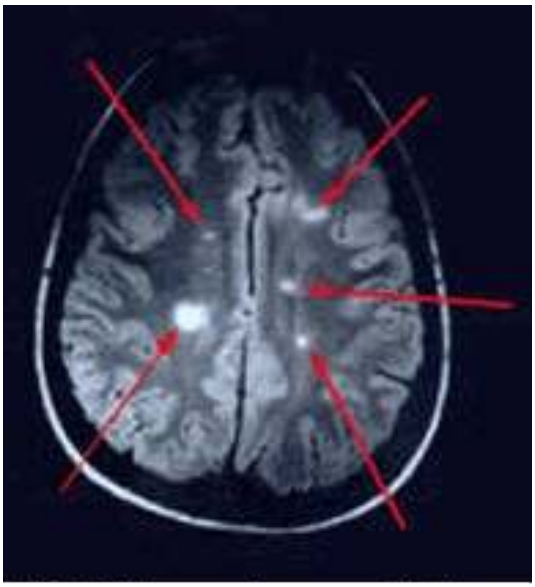
- Demyelination leads to impaired transduction of AP between nerve cells resulting in neurological symptoms e.g. abnormal sensations, vision problems and muscle weakness

MS DIAGNOSIS: PLAQUES

- There is white matter and grey matter
- Grey matter is where the nerve endings are; where the neurotransmission happens
- White matter → are the glial cells that wrap around axon (oligodendrocytes)



This MRI scan shows multiple abnormal white areas that correspond to MS plaques.

- Glial cells are fatty – appear white on scan
- White matter is the tracts that run through spinal cord etc. connecting different grey matter parts of CNS
- Within the white matter is a large "plaque" of demyelination
- These plaques can lead to the clinical appearance of transient or progressive loss of neurological function.

MRI: MS plaques are multifocal and often appear over time, hence the clinical findings can be quite varied.

Multiple MS plaques = remyelination repair (glial scar)

White areas indicate areas of demyelination within white matter of the cerebral hemispheres.

Black = white matter

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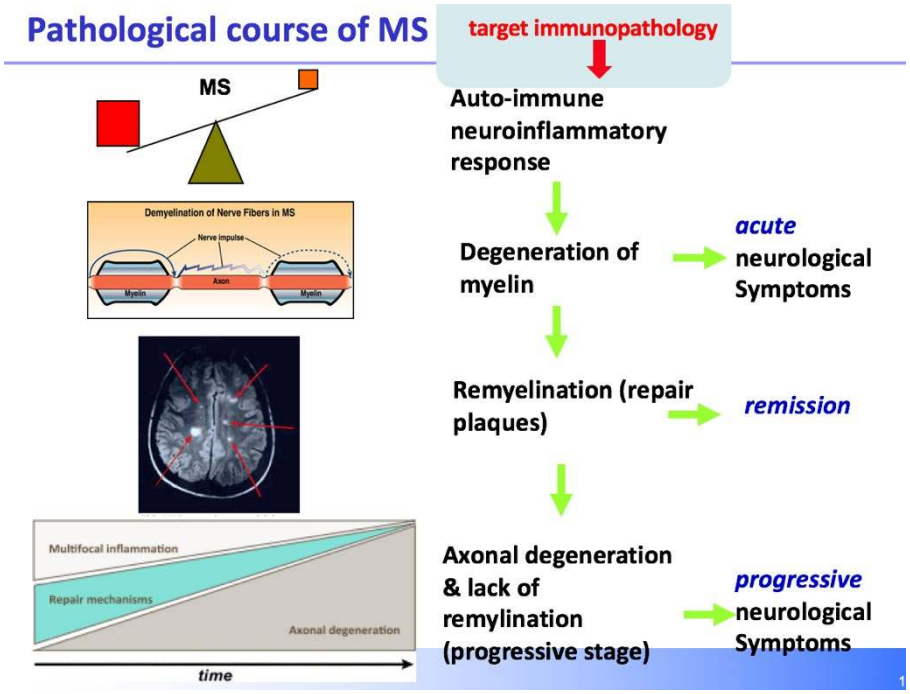
White spots = areas of demyelination within the white matter – indicate areas of high density of astrocytes (cells which should not be there) – THIS IS WHERE THE DAMAGE IS



PATHOLOGICAL COURSE OF MS:

- A time phase pathology
- Better to keep patient in the relapsing-remitting phase of MS, as it keeps the patient stable – you want to keep patient in remission, to stop the damaging/degeneration – to keep the symptoms stable
- When patient goes into progressive – not many drugs can slow this phase down

TIMELINE OF MS:

- At first you get multifocal inflammation; T cells infiltrate and activate microglia to attack the myelin

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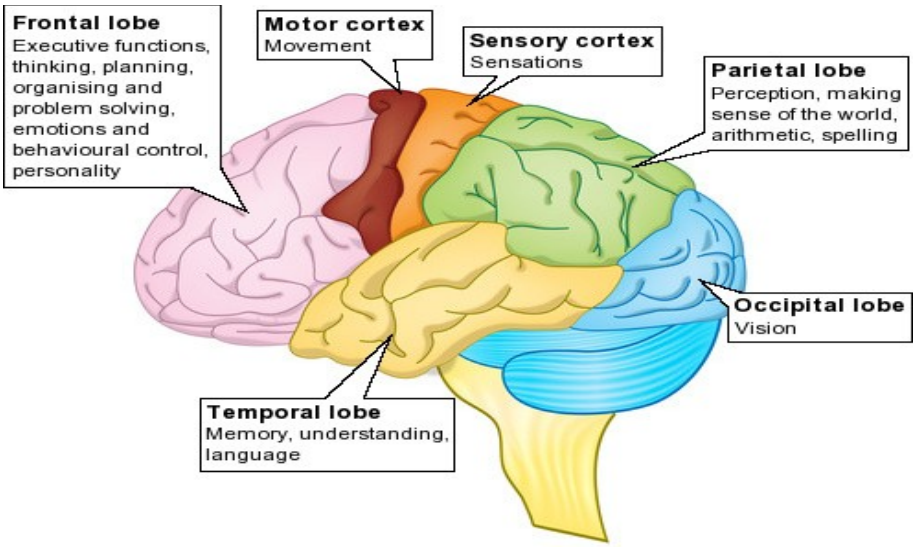
- It is an autoimmune disease in CNS
- A large component of the pathology of MS is inflammation (driven by T cells) and repair mechanisms (remission)
- PATHOLOGY: INFLAMMATION AND REPAIR
- Remyelination is in the form of plaques/scars – then goes into remission
- Over time the disease becomes **less about inflammation, the repair mechanism is not as efficient** (less repair) and then the axons are exposed and undergo degeneration (DURING THE PROGRESSIVE STAGE)
- Get more neurodegeneration and less inflammation during progressive stage

RELAPSE AND REMITTING → DRIVEN BY INFLAMMATION, REPAIR, KEEPING PATIENT IN REMISSION: DRUGS KEEP PATIENT IN RELAPSE AND REMITTING STAGE RATHER THAN PROGRESSIVE STAGE

MOST COMMON SITES OF DEMYLEINATION IN MS: where do these plaques form?

- Cerebral white matter
- Brain stem – **scar may form in brain stem – leads to neurological symptoms**
- Cerebellar tracts
- Optic nerve
- Spinal cord



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COMMON SITES OF PATHOLOGY AND CLINICAL SYMPTOMS:

OPTIC NERVE → patients commonly present with symptoms linked to optic nerve

- Central loss of vision, double vision, topic neuritis, uveitis

CEREBRAL CORTEX

- Intellectual impairment, memory loss

SPINAL CORD

- Sensory loss, muscle weakness

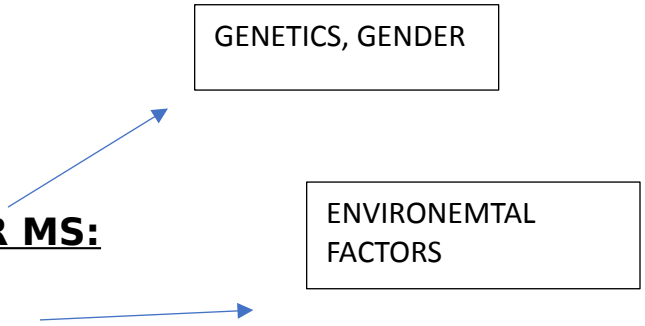
CEREBELLUM OR SPINOCEREBLLAR PATHWAYS

- Ataxia-stance and gait

BRAIN STEM

- Vertigo

RISK FACTORS FOR MS:



GENETICS, GENDER:

- Gender: MS is 2-3 times more likely in women than men
- Family history: increases risk of developing MS
- Race: more common in Caucasians

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- There is no direct genetic cause – there is no causative gene, but there are risk genes
- Risk gene alleles (MHC class II, ApoE ε4, CNTF deficiency)

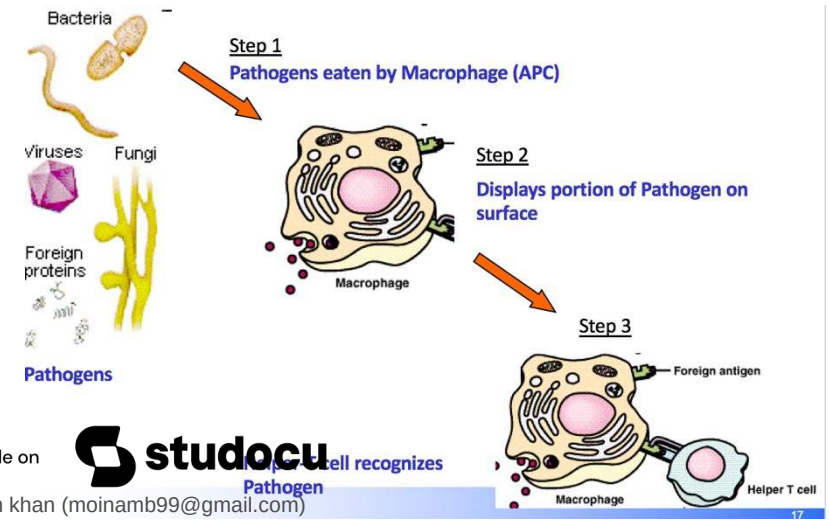
ENVIRONMENTAL FACTORS (EPIDEMIOLOGICAL STUDIES)

- Demographic: most common in those living in northern temperate climates (possibly Vitamin D levels, sun exposure?)
- Migration: the age at which you move is an important factor. If you migrate before the age of 15 your risk is that of people in the country, you move to. If you move after the age of 15, your risk stays fixed at that of the country you grew up in.
- Infections e.g. Epstein-Barr virus; autoimmune diseases are provoked by infection in people at genetic risk.
- Although no reliable isolation of infectious material from MS.
- Vitamin D levels can be protective

ADAPTIVE IMMUNE RESPONSE IN PERIPHERARY:

- MS is an autoimmune disease – prototypic neuroinflammatory disease which is driven by T cells – TH1 AND TH17 (lymphocytes) → **activate microglia** – kill of myelin cells
- T cells have to get INTO the CNS – have to cross BBB (they have to be **activated** in some way before they get into the CNS)
- Naïve T cells float around and cross BBB – but first step has to be some kind of **adaptive immune response – T cell response**

1. **Pathogens are recognised by APC (macrophage) circulating in blood**
2. **Macrophage engulfs the pathogen (phagocytic)**



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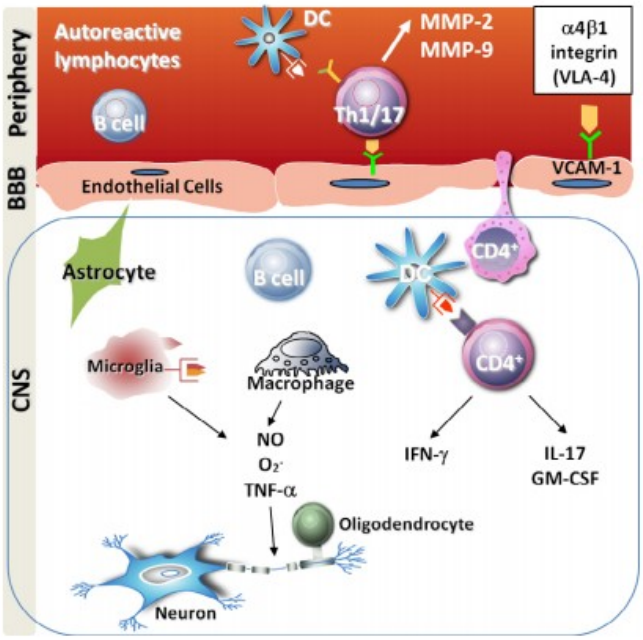
3. **On the surface of APC; displays a portion of pathogen to present to T cell (recognised via receptors) – T CELLS ACTIVATED**

IMMUNOLOGY OF MS: driven by TH1 AND TH17



- Periphery: in the blood
- BBB has tight junctions between it; it is not leaky like normal blood vessels – it is protective
- In the periphery there is some kind of infection – we need to have an adaptive immune response in the periphery
- APC will activate a CD4+ Type 1 cell – this leads to a T-helper cell response
- TH1 and TH17 activated by APCs in blood → when these are activated, they differentiate/divide
- TH1 → releases interferon gamma cytokine
- TH17 → releases interleukin 17 (IL-17) cytokine
- Adhesion molecules produced → integrin – it is expressed on the surface of T cells → ADHESION MOLECULES BECOME STICKY – they stick to the endothelial cells on BBB
- VCAM-1: vascular adhesion molecule 1
- T cells are stuck down to BBB endothelial cells
- BBB becomes 'leaky' → T cells get into CNS

1. ADAPTIVE IMMUNE RESPONSE
2. T cells differentiate/divide

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3. Express adhesion molecules
4. Stick down to endothelial cells
5. Interaction between endothelial cells and T cells
6. Migrate across BBB due to adhesion
7. T cells in CNS

- Once T cells in CNS: they have 2 roles – stimulate B cells and they are phagocytic cells.

In periphery infection activates adaptive response

- Dendritic (APC) cells activate a CD4+ Th1, Th17 cell mediated response
  - leads to CD4+ T cell differentiation and activation of Th1 releasing IFN and Th17 releasing IL17
  - migration across leaky BBB via a4B1 adhesion

In CNS

- pro-inflammatory Th1 and Th17 cells are re-activated by infiltrating APCs
  - activate microglia (critical for inflammatory demyelination in MS)
  - activation of B cells (autoantibodies against myelin)

MS IS DIVERSE SO TREATMENT IS CHALLENGING:

- MS varies greatly among individuals during the disease course
- Frequency and severity of relapses

Primary symptoms (neurological e.g. paralysis)	due to neuroinflammatory demyelination (relapse)
Secondary symptoms (e.g. incontinence, bedsores)	complications that arise from primary symptoms
Tertiary symptoms (e.g. depression)	social and psychological that arise from primary and secondary symptoms

3 categories of treatment plan	
1. Reduce the relapse and induce remission (early intervention)	Anti-inflammatory (short term therapy)
2. Limit and prevent new relapses (early intervention)	Immunotherapy (long term therapy) (immunomodulation, immunosuppression and immune-selective intervention)
3. Treatment of secondary and tertiary symptoms	Anti-depressants, stimulants (for fatigue), muscle relaxants (spasticity)

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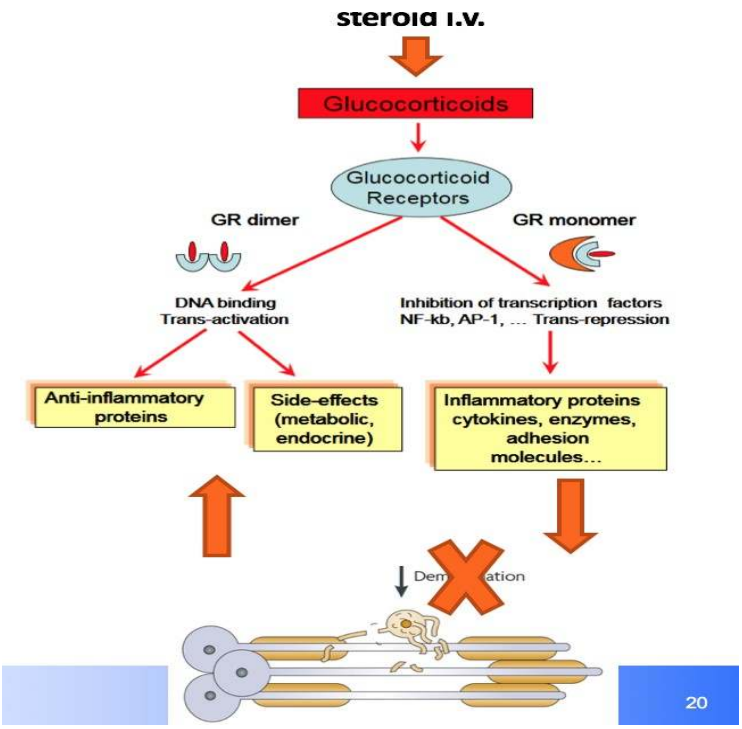
- Extent to which recovery (remission) is made from these attacks

- Progression of the disease into SP phase

1. REDUCE RELAPSE AND INDUCE REMISSION (ANTI-INFLAMMATORY):

- Steroids are useful for inflammatory diseases
- **Short term steroids** e.g. dexamethasone. Methylprednisolone (iv for 3-5 days)
- Reduce inflammation in the plaques of demyelination
- Induce remission and shorten duration of relapse
- Cannot give steroids for long term (as it can cause immunosuppression, bone thinning, weight gain, diabetes)



STEROIDS – activate on glucorticoid receptors – stimulate anti-inflammatory proteins

→ this limits damage to myelin cells

2. LIMIT AND PREVENT NEW RELAPSES: 5 TYPES OF IMMUNOTHERAPY

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Table 1 Characteristics of the five distinct types of immunotherapy for treatment of multiple sclerosis [18,20,115–117]

Characteristic	Immunomodulation	General immunosuppression	Immune-selective intervention – blockade type	Immune-selective intervention – sequestering type	Immune-selective intervention – depleting type
Representative class member/s	Interferon-β, glatiramer acetate, dimethyl fumarate, teriflunomide	Mitoxantrone, cyclophosphamide	Natalizumab	Fingolimod	Alemtuzumab
Mechanism of action	Pleotropic, net anti-inflammatory effect	Unspecified inhibition of cell proliferation	Specific inhibition of cell migration via integrin blockade	Sequesters autoreactive lymphocytes in lymph nodes and has a direct effect on CNS cells	Specific on lymphocytes
Efficacy	Moderate	Good	High	Good	High
Effect on immune competence	None in general, although possible with dimethyl fumarate	Given	No general immunocompromise but increased risk of JC virus infection	No general immunosuppression but increased risk of primary infection with herpes viruses	Given

- Immunomodulation therapies are often first line treatment – have broad mechanism action - alter cytokine levels
- General immunosuppression therapies → Mitoxantrone is used as a last resort where patients are not responding to any other immunomodulatory.

Then there are 3 types of immune-selective interventions:

- Blockade type – blocks T cells

- Sequestering type – stops T cells trapping through thymus – it REDUCES the number of T cells in blood

- Depleting type – selectively depletes T cells

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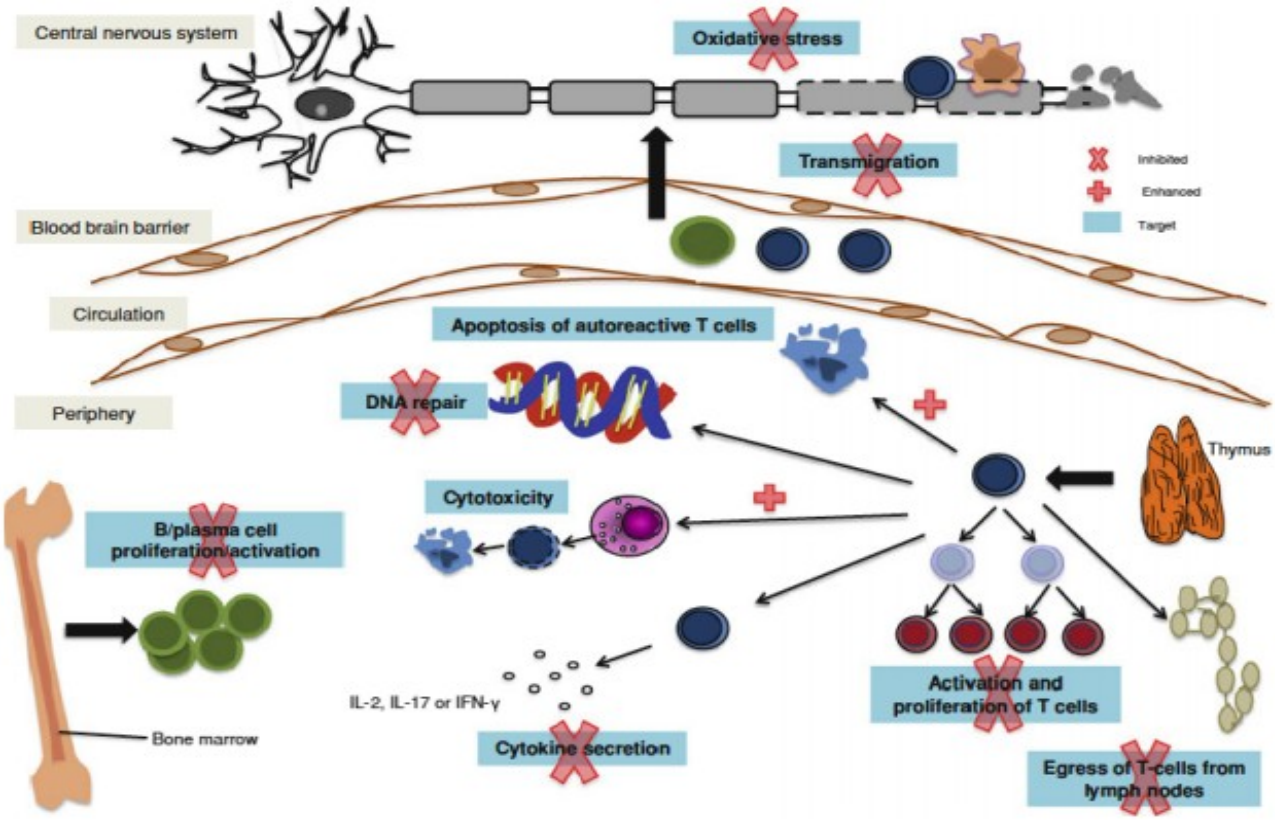
IMMUNOMODULATORS PLEITROPIC EFFECTS (act on all cytokines):



INTERFERONS, GLATIRAMER, DIMETHYL FUMARATE, TERIFLUNOMIDE

- Pleotropic effects: alter cytokines (e.g. ↓IFNg, ↓NFKB, ↑Th2 profile on T cells and microglia, ↑ NRF2), reduce T cell proliferation, adhesion molecules and prevent migration of activated T cells across BBB
- Partial efficacy as some activated T cells still enter CNS

COMMON S/E OF IMMMUNOMODULATORS:

- Typical flu-like symptoms: headache, fever, muscle aches
- Irritation at the injection site

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- Lower risk of infections compared to chemotherapy-like drugs (mitoxantrone) as more limited effects effects on the immune system

IMMUNOSUPPRESSANT: E.G. MITOXANTRONE

- Only if refractive to first line treatments
- Damages DNA preventing T/B cell division
- Reduces relapse rate and shows disability

SIDE EFFECTS:

- Immunosuppression (bone marrow depression)
- Cardiac toxicity

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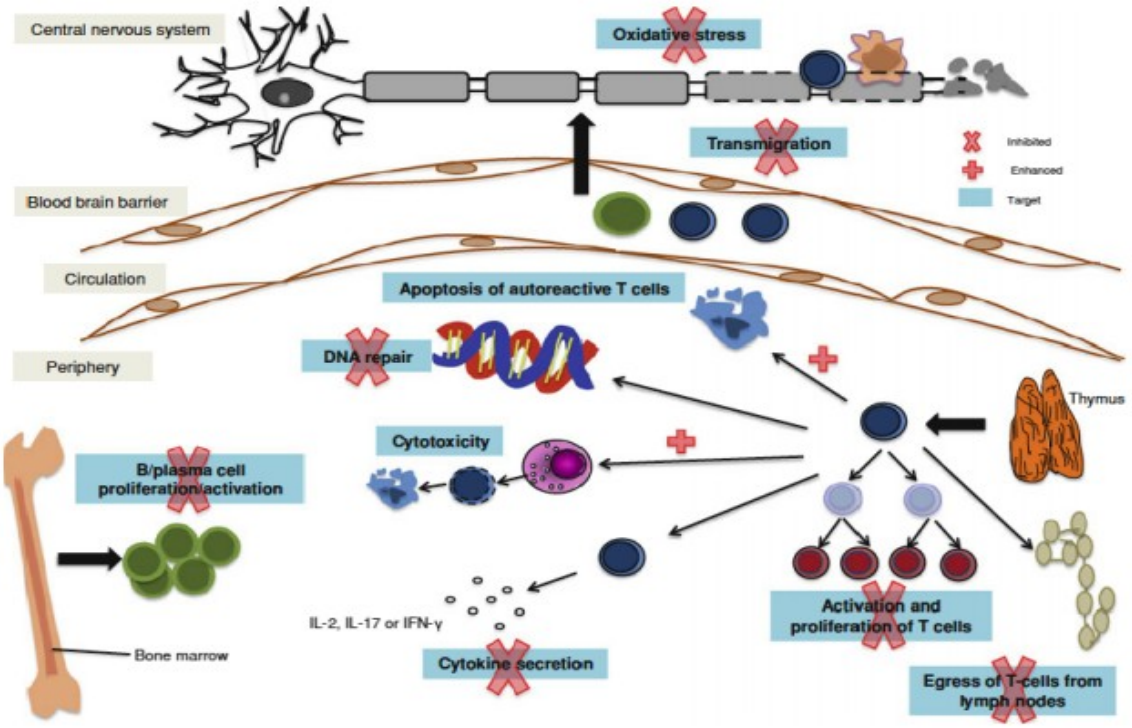
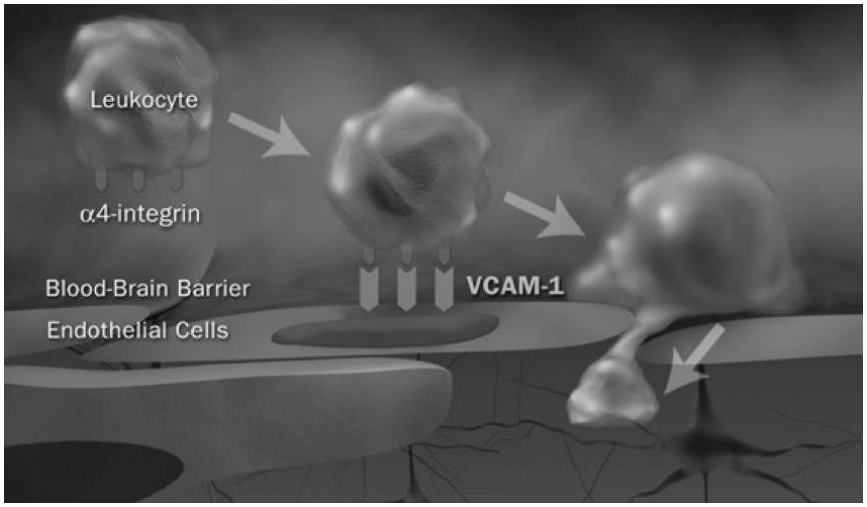


IMMUNE SELECTIVE – T CELL BLOCKAGE OF MIGRATION:

e.g. Natalixumab (Tysabri)

- Has a specific immune selective mode of action
- It specifically blocks T cells getting across Blood Brain Barrier
- α4-integrin plays *a central role* in Th1/Th17 cell adhesion and migration in RR (relapse and remission) MS
- High expression of this integrin specifically binds to this cell adhesion



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molecule on the endothelial cells to stick and move across BBB.

- Natalixumab is a humanised monoclonal antibody that binds specifically to integrin – so that the T cells cannot bind to the endothelial cells- they cannot migrate across the T cell (which is what would normally happen in MS) – so microglia are not activated – then there is no degeneration of myelin cells

- Nataluzimab reduces relapse rate and likelihood of developing a fixed disability compared with Interferon Avonex

Pivotal trials of natalizumab (tysabri): 2 year results

Drug	Phase	N	Reduction in relapse rate	Reduction in probability of acquiring fixed disability	Adverse effects
Tysabri *versus* placebo (AFFIRM)	III	942	67%	42% (17% *vs.* 29%)	
Tysabri & avonex *versus* avonex alone (SENTINEL)	III	1171	41% (0.34 *vs.* 0.75)	24% (23% *vs.* 29%)	PML in 2 cases (1 death)

NATALIZUMAB:

- Humanised monoclonal antibody to α4integrin (α4integrin antagonist)
- Relapses reduced by > 60% and slowed disease progression

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- For Patients with high disease activity despite treatment with beta interferon or patients with rapidly evolving severe rrMS
- Natalizumab is administered by intravenous infusion; the recommended dose is 300 mg every 28 days. Natalizumab costs £1130 per 300 mg vial (according to the manufacturer's submission), so over a year the cost of the drug is approximately £14,730 per patient.
- Withdrawn from market (2004) shortly after approval due to 3 cases of PML (progressive multifocal leukoencephalopathy)
- Global immunosuppression led to flare up of a latent JC viral infection leading to profound fatal CNS inflammation
- Now back on market (2006) with strict monitoring

IMMUNE SELECTIVE: T CELL SEQUESTERING IN LYMPH NODES

- E.G. FINGOLIMOD
- Keeps the T cells in the thymus (where T cells are produced)
- Fewer T cells circulating in the blood – fewer T cells crossing BBB
- Acts on S1P1 receptors
- It is an agonist on S1P1 (3, 4 and 5)
- T cells express a high number of S1P1 receptors

FINGOLIMOD was first available Oral treatment for Relapse and Remission MS:

- FTY720-Pacts as a non-selective, high affinity, reversible S1P agonist (S1P1, 3,4,5 agonist) induces internalisation and degradation of S1P1 receptors (functional antagonist)

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- The lack of S1P1 receptors mean T cells cannot respond to the S1P gradient and exit the lymph nodes reducing circulating T cells
- Prescribed when patients have had beta interferon treatment for a year but still have as many or more relapses than the year before, or relapses have continued to be severe.
- Prescribed when patients have had beta interferon treatment for a year but still have as many or more relapses than the year before, or relapses have continued to be severe.
- Most common side effects include influenza virus infections, headaches, diarrhoea and elevated liver enzyme activity.
- 'macular oedema with or without visual symptoms has been reported in 0.4% of patients treated with fingolimod 0.5 mg, occurring predominantly in the first 3–4 months of therapy. An ophthalmological evaluation is therefore recommended at 3–4 months after treatment initiation'.
- Fingolimod is given as a 0.5 mg oral dose once daily. Costs £1470 for 28 capsules equivalent to an annual cost of approximately £19,169 per person.

- THE DRUG IS A FUNCTIONAL AGONIST – IT CAUSES THE RECEPTOR TO INTERNALISE, SO IT NO LONGER IS ON THE OUTSIDE. THE EMDOGENOUS MOLECULE CAN NO LONGER BIND

IMMUNE SELECTIVE T/B CELL DEPLETION:

E.G. ALEMTUZUMAB (LEMTRADA)

- Anti-CD52 depletes naïve T cells and B cells that share the CD52 marker
- T-regulatory cells are preserved due to their low expression of CD52
- Delay (months) in the repopulation of pathogenic T and B cells. – not affected – so does not have much immunosuppression
- CD52 is a protein
-

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- Prescribed when patients active rrMS
- Equally effective as Natalizumab and Fingolimod.
- The recommended dosage of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 treatment courses. The initial treatment course lasts 5 consecutive days, followed 12 months later by the second treatment course of 3 consecutive days.
- Adverse reactions for alemtuzumab: autoimmunity (immune thrombocytopenic purpura, thyroid disorders, nephropathies [kidney diseases or damage], cytopenias [reduced blood cell numbers]), infusion-associated reactions, rash, headache, fever and respiratory tract infections.
- The price of alemtuzumab is £7045 per 12 mg vial, which equates to £56,360 for the full course of treatment consisting of 5 daily consecutive 12 mg doses in year 1, followed by 3 daily consecutive 12 mg doses 12 months later in year 2.

REDUCE SECONDARY/TERTIARY TREATMENT:

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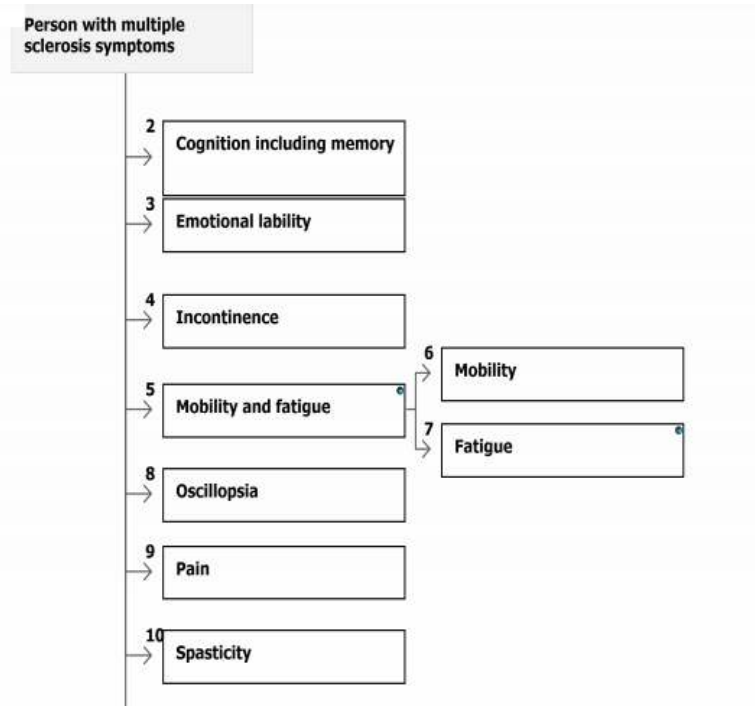

Anti-depressants, stimulants (for fatigue), muscle relaxants (spasticity)

NEW AND FUTURE TREATMENT FOR RELAPSE AND REMISSION MS AND PROGRESSIVE MS:

Disease modifying MS Drug	Approval	Route	Mechanism of Action
Daclizumab Zinbryta® Approved for organ transplantation Withdrawn in 2018 for rrMS (liver toxicity)	2017 Withdrawn 2018	iv	Humanised Anti-CD25 (specific depletion of B/T cells)
Rituximab Approved for lymphoma (1997)	Off label	iv	Chimera Anti-CD20 (B cell depletion, used off label for RR MS cases, PML risk)
Ocrelizumab	2018	iv	Humanised Anti-CD20 (specific depletion of B/T cells) *approved for primary progressive in US

Ocrelizumab has been indirectly compared to effective alemtuzumab and natalizumab and is as effective. It is more costly than alemtuzumab, so can only be recommended as an option for rrMS in adults with if alemtuzumab is contraindicated or otherwise unsuitable.

- New treatments need to have a better safety window than the existing immune selective treatments.
- The development of therapies for patients with progressive MS remains a significant challenge.

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SUMMARY:

- While all these new disease modifying treatments for RR MS are relatively effective at reducing new MRI lesion formation and relapse rates, they are broadly anti-inflammatory and often associated with side effects.
- Long term side effects on RR MS neurological disability are still unclear
- New therapies capable of targeting inflammation relevant only to the CNS are needed.
- The development of therapies for patients with progressive MS remains a significant challenge and a key unmet need.
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